**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re PATENT Application of
Flad

Group Art Unit: 1635

U.S. Serial No. 09/700,906

Examiner: Schultz

Filed: February 26, 2001

For: ANTISENSE OLIGONUCLEOTIDES FOR TREATMENT OF PROLIFERATING CELLS

**RULE 132 DECLARATION**



Hon. Assistant Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, Dr. Martin Hauses, declare and state as follows:

1. I am currently employed by Faustus Forschungs CIE. Translational Cancer Research GmbH. My present position and title are Project Manager Gene Therapy.

2. I have been continuously employed since 1992. During that time I have held the following positions with:

1992 - 1996 Scientist at the Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus in Frankfurt am Main

1996-1998 Scientist at the University Hospital of the Johann Wolfgang Goethe-University, Dept. of Hematology

1998-2001 Head of the Molecular and Cell Biology Laboratory at the University Hospital of the Technical University of Dresden, Dept. Surgical Research

since 2001 Projekt Manager at Faustus Forschungs Compagnie, Translational Cancer Research GmbH in Leipzig

3. I am the author or co-author of many articles related to the field of molecular and cell biology. A list of these articles is shown in Attachment 1.

4. I have read and understood the present patent application. I have also read and understood the Office Action(s) and the cited prior art in the present patent application.

5 I supervised the following experiments.

***In vivo* studies**

**Materials and Methods**

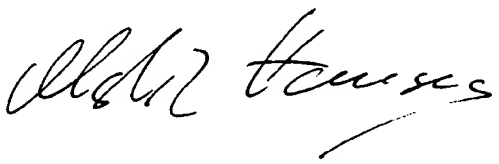
$1x10^6$ MB-49 (female C57B6-mice 6-8 weeks old) or $1x10^5$ RM-11 (male BALB/c-mice 4-8 weeks old) cells were injected subcutaneously into the lower left flank of mice. ODN were continuously delivered over a 14-day period (0,25µl/h) via miniosmotic pumps (ALZET, Alzet, Palo Alto, CA, USA) prefilled with ODN in saline solution and inserted subcutaneously into a paraspinal pocket under katamin or pentobarbital anesthesia. Tumor size was measured every second day with a caliper rule. Tumor volumes were calculated as $\Pi/6\ ab^2$ (a=longest, b=shortest tumor diameter). Each experimental condition included at least five animals per group. Animals were sacrificed at a tumor volume of more than 3000 $mm^3$ (RM-11) or 1300 $mm^3$ (MB-49). Statistical analysis was performed with SPSS® software. The animal studies were approved by the institutional and governmental review boards.

**Results**

To determine the effects of Ki-67 antisense treatment on tumor growth in vivo, two syngeneic subcutaneous tumor models with different genetic background were used, the MB-49 bladder tumor model in C57/B6 mice and the RM-11 prostate adenocarcinoma model in BALB/c mice. Oligonucleotides in saline were delivered continuously by subcutaneous mini-osmotic pumps. Pumps were implanted 24 hours after tumor cell injection. The tumor growth was significantly reduced in antisense ODN-

treated RM-11 tumors (p=0.05. Rank sum Man Whitney) and MB-49 tumors (p=0,001). Red and white blood cell counts and platelet numbers in ODN-treated mice showed no significant difference between antisense- and control-treated animals. Treatment of mice resulted in all groups in a moderate increase of spleen weight (data not shown).

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By 

Date: 13. March 2003

Attachment 1

Krex D, Hauses M, Appelt H, Mohr B, Ehninger G, Schackert HK, Schackert G.
Physical and functional characterization of the human LGI1 gene and its possible role in glioma development.
Acta Neuropathol (Berl). 2002 Mar;103(3):255-66.

Krex D, Mohr B, Hauses M, Ehninger G, Schackert HK, Schackert G.
Identification of uncommon chromosomal aberrations in the neuroglioma cell line H4 by spectral karyotyping.
J Neurooncol. 2001 Apr;52(2):119-28.

Brust P, Haubner R, Friedrich A, Scheunemann M, Anton M, Koufaki ON, Hauses M, Noll S, Noll B, Haberkorn U, Schackert G, Schackert HK, Avril N, Johannsen B.
Comparison of [18F]FHPG and [124/125I]FIAU for imaging herpes simplex virus type 1 thymidine kinase gene expression.
Eur J Nucl Med. 2001 Jun;28(6):721-9.

Hauses M, Schackert HK.
Gene therapy of malignant tumors
Zentralbl Chir. 2000;125 Suppl 1:41-6. Review. German.

Hauses M, Schackert HK.

Gene therapy and gastrointestinal cancer: concepts and clinical facts.

Langenbecks Arch Surg. 1999 Oct;384(5):479-88. Review.

Hauses M, Tonjes RR, Grez M.

The transcription factor Sp1 regulates the myeloid-specific expression of the human hematopoietic cell kinase (HCK) gene through binding to two adjacent GC boxes within the HCK promoter-proximal region.

J Biol Chem. 1998 Nov 27;273(48):31844-52.

Becker S, Wasser S, Hauses M, Hossle JP, Ott MG, Dinauer MC, Ganser A, Hoelzer D, Seger R, Grez M.

Correction of respiratory burst activity in X-linked chronic granulomatous cells to therapeutically relevant levels after gene transfer into bone marrow CD34+ cells.

Hum Gene Ther. 1998 Jul 20;9(11):1561-70.